Number 2

Health Technology Assessment

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U.S. Department of Health and Human Services
Public Health Service
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Foreword

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Laboratory Tests in End-Stage Renal Disease Patients Undergoing Dialysis

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A number of toxic products accumulate in the blood of individuals with renal failure, resulting in a complex syndrome called uremia. This condition, if untreated, is uniformly fatal. The first therapeutic attempt in humans to remove these toxic wastes from the blood by dialysis was reported in 1925.[1] However, it was not until the mid-1940s that a number of technical developments made possible the first successful renal dialysis (RD). Many further refinements were necessary to make RD an effective and practical medical therapy. These included the development of arteriovenous shunts for vascular access in 1960 and continuous improvements in dialyzer machinery, membranes, and dialysis solutions.[1,2] However, RD remains a complex, expensive, and labor-intensive endeavor. Because the costs of RD and renal transplantation (RT) were beyond the resources of most individuals with end-stage renal disease (ESRD) and because death would result if these modalities of treatment were not used, Congress amended the Social Security Act in 1972 to provide Medicare coverage for all patients with ESRD,[3] including coverage for RT as well as for long-term RD. This program is administered by the Health Care Financing Administration (HCFA) and has provided comprehensive therapy and diagnostic facilities for patients with chronic renal failure. There are 200,000 patients with ESRD being treated at a cost of more than $7 billion a year.[3]

A variety of laboratory tests were deemed necessary to monitor the clinical course of patients and the effectiveness of RD; these are listed in HCFA's *Medicare Coverage Issues Manual*.[4] Such tests include a category called "other than routinely performed" and comprise nerve conduction velocity tests, electrocardiograms (ECGs), chest x-rays, and tests for hepatitis-associated antigens. The purpose of this assessment is to reassess the clinical usefulness, necessity, and frequency requirements for these four tests in ESRD patients who are undergoing RD. A previous ESRD assessment[5] was published in 1986 by the Office of Health Technology Assessment. It evaluated some of the tests conducted on ESRD patients.

Background

Patients with ESRD and uremia develop a myriad of medical conditions, symptoms, and metabolic and physiologic disorders.[6] Among the metabolic conditions is an increased concentration in the blood and body fluids of a number of substances that are ordinarily removed by the normally functioning kidney. These include molecules of very low molecular weight such as urea (60 d) and creatinine (113 d), which are products of metabolism. A variety of higher molecular weight molecules, in the range from 300 d to 2,000 d, called middle molecules (MMs) also accumulate and cause various deleterious effects. These MMs are less efficiently removed by RD than are molecules of very low molecular weight. At least 25 different molecules have been identified as being potentially toxic. Which of these molecules, or combination of molecules, is responsible for particular symptoms is not known with precision.[6] The physiologic derangements, signs, and symptoms associated with ESRD can be treated by transplantation of a normal human kidney, or by RD, of which there are two types: hemodialysis (HD) and peritoneal dialysis (PD).

In HD, the patient's blood is pumped out of the body into a semipermeable, tubular dialyzer membrane with a large surface area. A physiologically normal dialysate solution circulates on the outside of this membrane. The abnormally high concentrations of the toxic, lower molecular weight solutes in the blood can pass through pores in the semipermeable membrane into the surrounding dialysate and can thereby be removed from the blood and interstitial fluids of the patient. The larger solutes that are normally present remain within the membrane; however, some undesirable MMs are also retained.

The elimination of toxic solutes also can be accomplished by PD. In this type of dialysis, the dialysate is infused into the peritoneal cavity and is

then removed; the peritoneal membranes act as the semipermeable membrane barrier, thus eliminating the excess solutes that are present in the blood and interstitial fluids.

It should be noted that PD removes a different spectrum of molecules than does HD and that some of the symptoms not relieved by HD can be relieved by PD.[7] However, although HD and PD are life-saving procedures,[6] not all symptoms of ESRD are relieved by these treatments, because the kidney provides more complex functions than does dialysis and because there are a large number of MMs not removed by dialysis. The duration and frequency of HD and the type of membrane and dialysate used in the particular HD procedure can affect the success of HD.

In the early years of dialysis therapy, most patients received the same dialysis prescription (DP). The DP includes factors such as the time on dialysis per session, the number of sessions per week, the composition of the dialysate, and the type of membrane used. Technical improvements allowed the average treatment time on dialysis for each session to decrease from 8 to fewer than 3 hours. The progressive reduction evolved from empiric trial and error and from the results of controlled studies.[8]

At this time, the optimal procedure for measuring the effectiveness of dialysis in a particular patient has not yet been established. This question is the subject of ongoing investigations and clinical trials. Thus, at this time, measuring a "dose" of dialysis and prescribing a particular regimen of dialysis are still largely empiric exercises. In addition, an individual with ESRD may have a variety of symptoms, and no single laboratory test or combination of tests can necessarily correlate with these symptoms.

A large, multi-institutional study, the National Cooperative Dialysis Study (NCDS), was funded by the National Institutes of Health (NIH) in 1974 to investigate these issues. The study involved eight centers and more than 150 patients.[9] It was a comprehensive trial that carefully measured the effects of various DPs and the concentrations of various solutes, including urea and creatinine, and related the results to patient outcomes. This study was performed between 1976 and 1981, and the results were published in final summary form in 1983.

Review of Available Information

The questions addressed in this assessment are whether certain laboratory and diagnostic procedures are clinically useful and necessary in patients with ESRD who are undergoing RD and with what frequency do the procedures need to be used. Tests of nerve function, tests for the presence of hepatitis-associated antigens or antibodies to such antigens, and the use of ECGs and chest x-rays in this patient population are being evaluated. The literature search included the use of DIALOG-MEDLINE, a computerized data base of the National Library of Medicine of English-language articles published between 1978 and 1992. A free text method of searching was used. The search was based on the words: "end-stage renal disease," "uremic neuropathy," and "uremia." These were in turn linked to the terms "hemodialysis," "neuromuscular conduction," "nerve conduction tests," "nerve conduction velocity," "ECG," "chest x-ray," and "hepatitis B testing." Two hundred sixty-one references were found. Of this group, 35 references addressed the issues in question, which were: the influence of nerve conduction tests (NCTs) and of neuropathic symptoms on the DP, the relationship between the patients' symptoms and NCT results, the data supporting ECGs or chest x-rays at regular intervals vs. for clinical cause, and the optimal testing strategy for hepatitis antigen B or antibody for the detection of hepatitis B infection in ESRD patients who are undergoing dialysis. In addition, standard textbooks[1,2] were used. Expert opinion also was sought, including responses to a *Federal Register* notice[10] regarding this assessment.

The only topic for which a substantial literature base exists is the subject of NCTs. The studies of NCTs are almost all case series. No articles were found in which the use of ECGs and chest x-rays in ESRD is the principal subject of the article or in which controlled studies measured the usefulness of these tests when performed at standard intervals. There were no controlled studies that directly addressed the optimal frequency of testing for hepatitis B antigens or antibodies. There is, however, a revised set of recommendations (see page 6) from the Centers for Disease Control and Prevention (CDC).

Before information regarding each of these specific tests is reviewed, certain general findings of the NCDS will be presented as a background for understanding

how the DP for individual patients is currently determined and for putting into context the reasons why certain tests may be needed.

The patients in the NCDS were divided into two groups, one with a time-averaged blood urea nitrogen (BUN) level held at 50 mg/dL and the other with a BUN level maintained at 100 mg/dL by the use of a single-pool, variable-volume kinetic model. Each of these groups was in turn divided into two groups of long- and short-time dialysis recipients. The average duration for the short-time dialysis was 3.25 hours, and 4.50 hours for the long-time dialysis. Patients who had high average BUN levels, independent of the duration of dialysis, had more frequent medical complications than did those whose BUN levels were kept low. Dialysis prescriptions that improved urea removal also improved patient outcome, regardless of the treatment's effect on higher molecular weight solutes.

Urea is presumed to serve as a marker or surrogate for more toxic substances which, like urea, diffuse across dialyzer membranes. To date, no candidates for this toxicity have been clearly identified and no single toxin has been identified with any particular symptom. It is likely that the pathogenesis of uremia is complex.[8] Thus, in 1993, after many years of intensive investigation, no one understands (on a molecular basis) exactly why patients benefit from dialysis.

The adequacy of dialysis is currently measured by various formulas and calculations that take into account the time on dialysis, the volume of distribution of urea in the patient's body, the rate of urea clearance by the dialyzer, the protein catabolic rate, and the time-averaged concentration of urea.[8] There is, at present, no consensus among experts as to how these various measurements and formulas are to be applied optimally in patients with ESRD. In an attempt to answer these questions, the National Institute of Diabetes and Digestive and Kidney Diseases will again fund a large multicenter trial to address the best methods for assessing the adequacy of dialysis. The goal of these studies will be to lower the morbidity and mortality of patients undergoing RD (Kusek J, NIH; personal communication, May 1992).

The first subject to be considered in detail is the use of NCTs in patients with ESRD. Peripheral neuropathy (PN) is a common manifestation of untreated uremia and is heralded by symptoms of dysfunction of the lower motor neurons or primary sensory neurons. Frequently observed features include muscle cramps and paresthesias, such as tingling or pricking in the toes and fingers. Depressed ankle reflexes and impaired vibration perception are early findings, and atrophy and weakness of the distal leg muscles may develop. The upper limbs are not as frequently affected.

The cause of neuropathy in ESRD is complex. There is evidence of both structural and functional abnormalities, including pathologic evidence for axonal degenerative lesions and demyelinization of the nerve fiber. The evidence for a functional disorder is the observation that, after RT, a very rapid recovery (within days) of nerve function can occur.[11] The physiologic disturbance in nerve function is assumed to be due to the toxic effects of MMs of unknown types.

Electrophysiologic investigations in patients with chronic uremia have demonstrated a slowing of conduction in all peripheral nerves studied. This slowing occurs to almost the same degree in motor and sensory nerve fibers. There is no critical degree of slowing of conduction to indicate whether clinical signs of neuropathy will appear. The measurement of vibratory perception thresholds (VTs), according to some observers, is more suitable for assessing the progression of recovery from uremic neuropathy than is the measurement of nerve conduction velocity.[12]

The questions are whether NCTs serve as a useful guide with regard to changing the DP, which of the several NCTs are best able to detect PN and correlate best with the patient's symptoms, and finally, how often these tests should be performed in patients undergoing RD.

Two recent textbooks[1,8] and a recent review article[13] that discuss in detail how the DP is determined do not describe nerve conduction studies as an important basis for altering the DP. There are no articles in the literature that use NCTs as the sole determinant of the DP, and there are only a few reports that directly compare the success of DPs that did or did not use NCT as a guide. All of these reports are case series that describe a number of different aspects of NCT in ESRD. These reports are heterogeneous in terms of the patient mix, the types of dialysis, and the measurement of nerve function. The information in these articles[14-30] is summarized in Table 1.

The tests used in the studies cited in Table 1 were those of motor and sensory nerve conduction times along peripheral nerves and of the H reflex, which measures the velocity of electrically elicited spinal

Table 1. The use of NCTs in patients with ESRD

Reference	Year	No. of patients	Type of NCT	Major findings	Was DP changed because of abnormal NCT or the presence of PN?	Relationship between neurologic symptoms and NCT	Relationship between renal functional tests, NCT, and symptoms
Ackil (14)	1981	17[a]	Late-response H reflex, F-wave responses, MNCV	29% had abnormalities in motor function, 12% in sensory function.	No	NS	No
Bonimimi (15)	1982	39[b]	MNCV	MNCV increased in patients in whom it was initially abnormal.[e]	No	NS	NS
Caccia (16)	1977	43	MNCV, SNCV	60% had PN.	No	NS	No
Codish (17)	1971	16	MNCV, SNCV	Initially, most patients had decreases in MNCV and SNCV; very little change after 1 y.	No	No	No
D'amour (18)	1984	15	MNCV, SNCV	Most patients had abnormalities, more in SNCV, 6/15 had PN.	No	NS	NS
Dyck (19)	1979	22[c]	Touch and pressure sensations, MNCV, SNCV	No correlation between results of NCT and degree of uremia.	No	No	No
Hallar (20)	1979	62	MNCV, SNCV, VT, H reflex	12/62 patients had clinical evidence of neuropathy; however, of 50 patients without PN, 30 patients had abnormal NCT.	No	56% of patients without PN had abnormal NCT	NS
Jebson (21)	1967	52[d]	MNCV, SNCV	In group 1, there was a relationship between renal function and NCT; in group 2, a patient on dialysis longer had increased NCV; in group 3, a single dialysis did not affect NCT.	Yes, in 3 patients in group 2	NS	Yes
Kominami (22)	1971	7[e]	MNCV	Large variations in MNCV were noted on a day-to-day basis in both patients and normal subjects.	No	NS	NS
Lindholm (23)	1982	15[f]	MNCV, SNCV, VT	Despite treatment, the patients' PN and NCT got worse after a mean observation period of 18 mo.	No	No	NS
Manohar (24)	1987	2	MNCV	Change in "MM profiles" correlated with decreasing PN.	Yes[g]	Yes	Yes[h]
McGonigle (25)	1985	4	MNCV	A typical NP with ascending lesions, no effect of changing DP.	Yes[i]	No	No
Nielsen (26)	1974	16[j]	MNCV, SNCV, VT	Dissociation between clinical findings and NCT, vibration tests are very useful.	No	No[k]	No
Preswick (27)	1964	20[l]	MNCV, SNCV	Dissociation between clinical findings and NCT.	NR	No	Yes
Techan (28)	1983	From the NCDS	MNCV, SNCV	Abnormalities in NCT were observed more often in patients with short dialysis times and high BUN.	NR	NS	Yes
Tegner (29)	1985	22 treated with HD, 21 treated with CAPD	MNCV, SNCV, VT	Test of NCV did not differ between the two groups. VTs were more abnormal in the CAPD group. Nerve function deteriorates in both types of patients but in different ways.	No	NS	No
Versacki (30)	1964	24	MNCV, SNCV	Clinical improvement seen with more frequent dialysis, no change in NCT.	No	No	No

[a]Twelve had no symptoms of PN; patients were children.
[b]Patients treated with HD and hemoperfusion in five different centers.
[c]Two treatment groups were used, a long-time treatment group and a short-time treatment group.
[d]Three groups: group 1, no dialysis; group 2, dialysis; group 3, studies just before and after a single dialysis.

monosynaptic reflexes along the entire length of the afferent and efferent pathways. The F wave test measures conduction times in the motor nerves to and from the spinal cord from the more proximal portions of the peripheral nerve pathways.[31,32] Other tests of sensory nerve function that are used are VTs, touch and pressure sensations, and current perception threshold tests.[19,20,26,28,31-33] Whether these tests are as useful in patients with ESRD as the more standard tests of nerve conduction velocities has not as yet been answered. According to some investigators, objective abnormalities often can be observed by the use of these tests, even when there are no clinical symptoms of neuropathy.[32]

These tests rely on complex equipment and procedures and are most reliable when they are performed by expert and experienced individuals. The roles of the professional and technicians in performing these tests have not been uniformly defined. The exact methods of performing these tests vary between institutions, and, therefore, each laboratory must establish its own control values.[31] Even within a single institution, there can be significant interexaminer differences in the results of NCTs.[34] Thus, comparing data between institutions may not be straightforward. Moreover, normal values are spread over a rather wide range, and tests performed on a daily basis for 10 days may reveal large variations.[22] Therefore, coming to a conclusion on the basis of results from a single test may be problematic. In addition, certain variables such as the age and the sex of the patient, as well as the limb surface temperature, also can affect the results.[31] There have been no randomized prospective trials comparing the usefulness of these different tests in patients with ESRD.

The 17 studies reported in Table 1 differ with regard to the types of NCTs performed, although all studies used tests of motor and sensory nerve conduction velocity. The patient population varied with regard to age, types of dialysis used, and dialysis or lack of dialysis. In 12 of the 17 studies, the DP was not altered because of the findings of the NCTs. A clear correlation between longer dialysis times and improvement in NCT was demonstrated in only two articles. In seven of the studies, there was no correlation between the findings of the NCTs and clinical symptoms; in eight reports, no statement was made regarding this relationship. In four reports in which the relationship between the results of renal function tests and NCTs or the presence of PN was examined, greater abnormalities in renal function were seen in those patients with PN and/or an abnormal NCT. No relationship was observed in eight reports, and in five reports, such a relationship was not mentioned. Thus, these studies fail to offer a convincing argument that the results of NCTs provide a useful guide for changing the DP or that NCTs should be performed on a routine basis for that purpose.

HCFA's *Medicare Coverage Issues Manual*[4] states that the testing for hepatitis-associated antigens will be reimbursed for each patient when performed once per month. In the late 1960s and early 1970s, patients and staff in dialysis centers were at considerable risk for hepatitis B virus (HBV) infections. However, with the advent of tests capable of detecting the presence of virus (i.e., the presence of hepatitis B surface antigen [HBsAg]) in the blood and their application in 1972 in routine blood banking, the chances of being infected by blood transfusion diminished (although outbreaks of HBV continued to occur in dialysis centers because of contaminated dialysis and other equipment). Because of this, CDC published guidelines in 1977[35] outlining a number of procedures and precautions to be taken to prevent the contamination of equipment by HBV. These procedures are known as Universal Precautions (UP) and are now widely used in health care settings. Since the adoption of UP, the incidence of HBV has decreased markedly among the patients and

(Table 1 footnotes — continued)

[e]Three patients not yet treated by dialysis.
[f]These patients were treated by CAPD.
[g]Patients improved after high-efficiency dialysis.
[h]Change in profile of MMs.
[i]Did not change course of PN.
[j]Patients were studied before and during HD.
[k]Abnormal NCTs were noted before clinical symptoms.
[l]Patients had ESRD but were not dialyzed.
Abbreviations: BUN = blood urea nitrogen; CAPD = continuous ambulatory peritoneal dialysis; DP = dialysis prescription; ESRD = end-stage renal disease; HD = hemodialysis; MM = middle molecules; MNCV = motor nerve conduction velocity; NCDS = National Cooperative Dialysis Study; NCT = nerve conduction test; NCV = nerve conduction velocity; NP = neuropathy; NR = not relevant; NS = not stated; PN = peripheral neuropathy; SNCV = sensory nerve conduction velocity; VT = vibration threshold perception test.
SOURCE: Compiled by the Office of Health Technology Assessment.

professional staff at dialysis centers. In addition to better control of infections, the widespread use of immunization of both patient and staff against HBV has further decreased its incidence in dialysis centers.[35]

An individual can be classified as to whether he or she is infected, immune, or susceptible to HBV by several serologic tests. The blood of an infected individual contains the HBV (that is, the individual is positive for the presence of HBsAg). The blood of an immune individual has an antibody to the HBsAg (anti-HBs-positive). A susceptible person is both HBsAg-negative and anti-HBs-negative.

In 1990, CDC provided revised recommendations for the screening of staff and patients in dialysis centers.[36] CDC recommended that all patients and staff be screened for HBsAg and anti-HBs when first entering the dialysis center. The schedule of future testing in these individuals would then depend on their serologic status and on whether they have been immunized against HBV (Table 2).

For individuals who are in the process of being immunized against HBV, CDC recommends the following:

> Patients and staff who are in the process of receiving hepatitis B vaccines, but have not received the complete series, should continue to be routinely screened as susceptible. Between 1 and 6 months after the third dose, all vaccinees should be tested for anti-HBs to confirm their response to the vaccine. Patients who have a level of anti-HBs of at least 10 sample ratio units (SRUs) by radioimmunoassay (RIA) or who are positive by enzyme immunoassay (EIA) are considered adequate responders to vaccine and need only be tested for anti-HBs annually to verify their immune status. If anti-HBs drops below 10 SRUs by RIA or is negative by EIA, a booster dose of hepatitis B vaccine should be given. Staff who have an adequate response to the vaccine need no further routine testing.[36]

Therefore, the test that should be performed on a particular individual with ESRD depends on the serologic status of the individual and whether he or she has been successfully immunized against HBV.

HCFA's *Medicare Coverage Issues Manual*[4] allows for ECG reimbursement every 3 months and for chest x-rays every 6 months. These tests are used to evaluate cardiovascular and pulmonary disease, respectively.

Cardiovascular disease accounts for about half of all deaths in patients with ESRD.[37] In order to determine if such patients need, and benefit from, ECGs and chest x-ray examinations on a regular basis without specific indications, it is necessary to know the type, frequency, and rate of their cardiovascular disease.

The types of cardiovascular disease that cause these deaths are shown in Table 3. These data are taken from a study of 1,453 patients treated by long-term HD over 6 years.[38] One hundred seventy-seven patients died during this period. Stroke accounted for 19.8% of these deaths; and few of the other cardiovascular events would have been diagnosed or prevented by the routine performance of ECGs.

Other data regarding the frequency of cardiovascular disease are available from the NCDS.[39] In 162 patients observed for 48 weeks, cardiac morbid events were observed in 24% (range, 11% to 44%) of the patients. The percentage was greater in those groups with shorter dialysis times and with a higher time-averaged level of BUN. Within 12 months after the study was completed, there were 16 deaths. In three patients, the cause was unknown; of the remaining 13 deaths, eight were attributed to cardiac causes. Thus, cardiovascular

Table 2. Recommendations for serologic surveillance for hepatitis B in hemodialysis centers[a]

Vaccination and serologic status	Frequency of screening HBsAg		Frequency of screening Anti-HBs	
	Patients	Staff	Patients	Staff
Unvaccinated				
Susceptible	Monthly	Semiannually	Semiannually	Semiannually
HBsAg carrier	Annually	Annually	None	None
Anti-HBs-positive[b]	None	None	Annually	None
Vaccinated				
Anti-HBs-positive[b]	None	None	Annually	None
Low level or no anti-HBs[a]	Monthly	Semiannually	Semiannually	Semiannually

[a]From reference 36 (recommendations provided by CDC).
[b]At least 10 sample ratio units by radioimmunoassay or positive by enzyme immunoassay.
Abbreviations: Anti-HBs = antibody to hepatitis B surface antigen; CDC = Centers for Disease Control and Prevention; HBsAg = hepatitis B surface antigen.

events occur frequently; however, no reports prospectively examined the usefulness of ECGs at specified intervals in ESRD patients for whom specific medical indications for ECGs were absent.

Pulmonary abnormalities are often found in patients with ESRD; one of these abnormalities is uremic lung, a form of pulmonary edema caused by a combination of ventricular failure and toxic factors that increase the permeability of the alveolar capillaries. Pleural effusions are often seen in such patients, but the exact cause has not been established. Hypoxemia and hypoventilation also are common in these patients, again, as the result of multiple causes. Patients undergoing PD have serious alterations in pulmonary function and gas exchange, in part because of the compression of the basal segments of the lung due to the distension of the peritoneal cavity by the dialysate. Complications such as chronic pleural effusion, atelectasis, acute hydrothorax, and bronchitis can occur.[40] No studies were found that examined specifically the effectiveness of routine chest x-rays in diagnosing or preventing disease or in improving outcomes in patients with these abnormalities.

As part of the assessment process, other agencies of the Public Health Service (PHS) were consulted. NIH provided comments from several different institutes. NIH stated that, from a scientific point of view, there is very little evidence at this time to support the utility of routine, periodic nerve conduction studies to monitor the efficacy of dialysis. The data, however, do not rule out the possible usefulness in some patients. Given the changes in dialysis techniques in recent years, the only way to answer the question definitively is with a comprehensive study.

Table 3. Causes of death in 177 patients treated by hemodialysis[a]

Type of cardiovascular disease	Total	
	n	%
Cardiovascular death	87	49.1
Stroke	35	19.8
Myocardial infarction	22	12.4
Congestive cardiac failure	17	9.6
Sudden death, cardiac rhythm abnormalities (except hyperkalemia)	7	3.9
Mesenteric infarction	3	1.7
Other vascular diseases (e.g., aortic dissection, arteritis)	3	1.7
Hemorrhagic pericarditis	3	1.7

[a]From reference 38.

NIH also stated that nerve conduction studies could be performed for clinical neurologic reasons, as indeed they frequently are. There would be no reason, and no basis in medical science, to continue a policy of monitoring nerve conduction studies solely to assess the adequacy of dialysis.

NIH commented that it is probably not necessary to perform ECGs every 3 months and chest x-rays every 6 months simply because the patients have ESRD. Rather, the frequency with which these tests are ordered should be dictated by the concurrent presence of cardiovascular disease sufficiently unstable to require ECGs as often as every 6 months and of pulmonary problems that would require chest x-rays every 6 months. Electrocardiograms every 3 months and chest x-rays every 6 months on a routine basis are more frequent than necessary and should require specific justification.

NIH indicated that chest x-rays and ECGs should be performed annually and that tests for hepatitis B antigens should be performed quarterly. Nerve conduction velocity tests should be performed as needed.

The Food and Drug Administration (FDA) stated, in regard to regulatory status, nerve conduction velocity devices are classified as class II under Section 882, 1550 of the Code of Federal Regulations. FDA stated there are eight devices in this category that may be legally marketed to measure nerve conduction velocity.

A number of responses were obtained from individuals and organizations; some were in response to the *Federal Register* notice[10] of this assessment. These are summarized in Table 4. Also, another response is provided in the text.

The response from the American Association of Electrodiagnostic Medicine (AAEM) is quoted more extensively because a division of NIH has indicated that their position does not substantially differ from that of the Association. The AAEM stated that:

> Uremia is a complex metabolic disorder, and PN is only one of its many clinical manifestations. The present use of nerve conduction studies (NCS) for monitoring dialysis seems to be based on the early experience with hemodialysis. Dialysis strategies, techniques, patient-mix, and equipment have evolved over the years to the point where present-day experience bears little resemblance to the clinical practices of the 1960s and 1970s. Consequently, the situation where NCS were a useful adjunct to standard dialysis practice in the early days may not

Table 4. Responses from groups and organizations

Correspondent	Institution	NCT	ECG and chest x-rays	Hepatitis B and other tests
Albers[a]	American Academy of Neurology, Ann Arbor, MI	Not required on a regular basis to evaluate the effectiveness of dialysis.	NS	NS
Wilbourn[b]	American Academy of Neurology, Cleveland, OH	Tests of nerve conduction velocity alone are worthless. NCTs in the broader sense are useful. These could be performed at intervals of 12-24 mo. The findings on clinical neurologic examination and patient's symptoms are a better means of following the patient's status. If, however, there is a major change in the patient's symptoms, then electrodiagnostic studies are indicated, and the findings of a baseline profile are useful.	NS	NS
Colangelo	Northeastern Nephrology Association, Rockville, CT	Rarely order NCT, only on patients with carpal tunnel syndrome or on an as-needed basis.	ECG only when clinically indicated. Chest x-rays only for clinical indications.	They follow the CDC guidelines of once per month with certain reservations. They believe test necessary at the time of initial therapy, less necessary on patients treated at home with PD.
White	Dallas Nephrology Associates, Dallas, TX	NS	They appear to be in favor of frequent ECGs.	They appear to be in favor of once-per-month testing.
Hakim	Vanderbilt University Medical Center, Nashville, TN	For patients with ESRD due to diabetes, NCT should be done every 6 mo; for other patients, once per year.	ECG, every 6 mo; chest x-rays, when clinically indicated.	Hepatitis B testing once per month; strongly supports "kinetic modeling" as a method of measuring the dialysis dose.
Finlayson	Nephrology Associates, Gainesville, FL	NCTs are important because of a high incidence of carpal tunnel syndrome. Twice-a-year NCTs are appropriate.	ECGs and chest x-rays twice a year are appropriate.	If patients are antibody-positive, they should be tested infrequently; if patients are negative, they require routine monitoring.
Slifkin	Queens Artificial Kidney Center, Queens, NY	NCT should be done regularly.	ECG, every 3 mo; chest x-rays, every 6 mo.	Should be done monthly. Urea kinetic studies also are helpful.
Sweet	NMC Division of National Medical Care, Inc., Springfield, MA	NCT should be done 2 times per year.	ECGs are helpful, exact frequency not given; chest x-rays should be obtained on a yearly basis.	Should be done monthly.
Rodriguez	Salick Health Care, Inc., Los Angeles, CA	NCT should be done 4 times per year; EEG testing, every 6 mo.	NS	NS
Ramenofsky	Tri-City Nephrology, Oceanside, CA	Should not be performed as routine tests.	Yearly intervals are sufficient unless there is a specific indication.	Less frequently than monthly may be sufficient. Urea kinetics should be used as a guide for the frequency of dialysis.
Massry	The National Kidney Foundation, Inc., New York, NY	NS	NS	Testing for hepatitis antigen should be performed once a month.
Bruno	Biotrax, Fairlawn, NJ	Testing twice a year is indicated.	NS	NS

Table 4. Responses from groups and organizations—continued

Correspondent	Institution	NCT	ECG and chest x-rays	Hepatitis B and other tests
Fuda	National Medical Care, Inc., Waltham, MA	Semiannual studies are appropriate; however, adequate testing (7-8 nerves) should be performed.	ECG at baseline and then semi-annually is necessary; semi-annual chest x-rays are advocated.	Follow CDC guidelines.
Steinman	Renal Physician Association, Washington, DC	Should be done only if clinically indicated.	ECG and chest x-rays once per year.	Hepatitis antigen and antibody testing can be done every 3-4 mo (unless clinically indicated). Urea kinetic modeling should be done monthly.
Arezzo	Albert Einstein College of Medicine, Bronx, NY	Should be done every 6 mo. Both velocities and amplitude should be measured in the distal sensory and motor nerves.	NS	NS
Dickmeyer	CHABOT Nephrology Medical Group, Inc., Castro Valley, CA	Once per year.	ECG should be done 4 times a year, chest x-rays on a regular basis.	Should be done monthly.
Suki	American Society of Nephrology, Baylor College of Medicine, Houston, TX	No evidence documenting the benefit of repeated examination; coverage once per year should suffice.	No evidence that routine ECG or chest x-rays are beneficial; they should be performed no more frequently than every 6 mo.	There is evidence to support the consensus that hepatitis B antigen testing should be done on a monthly basis.
Hallett	American Association of Electrodiagnostic Medicine, Rochester, MN	Data do not strongly support the use of nerve conduction studies in general. Therefore, a prospective study is needed.	NS	NS

[a]University of Michigan Medical Center, Ann Arbor, MI.
[b]The Cleveland Clinic Foundation, Cleveland, OH.
Abbreviations: CDC = Centers for Disease Control and Prevention; ECG = electrocardiogram; EEG = electroencephalogram; ESRD = end-stage renal disease; NCT = nerve conduction test; NS = not stated; PD = peritoneal dialysis.
SOURCE: Compiled by the Office of Health Technology Assessment.

pertain today. We do not know whether a change in NCS values is sufficiently sensitive to indicate a problem with dialysis. Given the fact that increasing numbers of diabetics are included in the ESRD population, we also do not know how specific a change in NCS values is for dialysis-related problems. Given this lack of knowledge and the clear need for reliable monitoring methods, it seems reasonable to propose that a protocol be designed to test the hypothesis that NCS are a reliable method to monitor the adequacy of dialysis.

Overall, the opinions from individuals and organizations were heterogeneous (Table 4). Some commented that the appropriate NCT schedules could be as frequent as every 3 months, chest x-rays every 6 months, and ECGs every 3 months. Other experts offered the opinion that all three tests should not be routinely performed but should be used only as specific clinical circumstances would dictate (and others recommended frequencies somewhere between these extremes). Nearly 50% of the advice for hepatitis B testing recommended that the CDC guidelines be followed or that the presence of hepatitis antigen calls for monthly testing.

Discussion

Renal dialysis for ESRD has been performed on large numbers of patients during the past 20 years. Despite this experience, the precise causes of the uremic syndrome are poorly understood, as are the precise reasons why RD improves the uremic state.[6,41] Also, the optimal amount of time on and method of RD are still under study; thus, the methods of determining the optimal prescription for RD in individual patients are still evolving, as are the definitions of adequate dialysis. In part, the reason for these gaps in knowledge is that "to date, no systematic guidelines for evaluating quality have been developed for the ESRD

program, and support for quality-assessment research in this area has been quite limited."[42]

Many tests (including the ones described in this assessment) are used to monitor and evaluate patients receiving RD. No large systematic study has been performed to evaluate the usefulness of many of these tests by rigorous, prospective, randomized trials. Indeed, a number of organizations have recommended that this be done. Therefore, high-quality data with regard to the usefulness and optimal frequency of NCTs, ECGs, chest x-rays, and tests for the presence of HBV are lacking.

The frequency of PN in patients with ESRD has markedly diminished during the past 30 years for several reasons. Patient access to dialysis has improved, as have dialysis techniques and methods by which the adequacy of dialysis can be evaluated.[8] The data in the articles summarizing the use of NCTs to examine patients undergoing RD (Table 1) do not support the thesis that NCT should be performed on a regular schedule. Rather, the majority of data suggests that such tests should be performed if and when the patients develop symptoms of PN. The frequency of NCTs in such patients should be determined thereafter by clinical circumstances on a case-by-case basis. Opinion from groups and individuals regarding the frequency of NCTs varied over a wide range. The response from PHS uniformly indicated that NCTs were not required on a routine basis, but rather that such studies be performed only for specific medical indications. The development of more clinical trials to investigate the usefulness of NCTs in patients with ESRD also was suggested.

In addition to the more commonly performed motor nerve conduction velocity and sensory nerve conduction velocity tests, various tests of sensory perception such as VT, touch and pressure tests, and current perception threshold tests also have been used by some physicians to measure sensory nerve function. Whether these tests provide the same information regarding sensory nerve function as do the former tests is not clear from the literature reviewed, nor is there any evidence that the results of such tests alone are useful in altering the DP.

The HCFA *Medicare Coverage Issues Manual*[4] guidelines allow for the performance of ECGs every 3 months and chest x-rays every 6 months (on a routine basis). There are no objective data to support the clinical effectiveness of such testing. The PHS response indicates that these tests should be performed for the clinical management of the patient in the presence of cardiovascular and pulmonary problems. PHS also indicated, however, that these tests should be performed on a routine basis once per year. Advice from individuals and organizations regarding these tests was not uniform, e.g., recommendations varied, from performing chest x-rays every 6 months to performing them on a regular basis or whenever needed. The range of recommendations for ECGs varied from every 3 months to whenever needed.

The recommended schedule of testing for hepatitis B antigens in HCFA's *Medicare Coverage Issues Manual*[4] was developed 12 years ago. At that time, only tests for hepatitis B antigens were performed; advances in this area since then have significantly altered ideas as to what tests should be administered and with what frequency. Tests for the presence of both HBsAg and anti-HBs are currently being performed. In 1990, CDC produced guidelines that encompass these new ideas for hepatitis B tested in various patient groups. These CDC recommendations[36] are shown in Table 2 and indicate that unvaccinated susceptible patients should be tested once per month for the presence of HBsAg. Also, CDC recommended that HBsAg carriers should be tested annually. Those patients who are anti-HBs-positive or who have been successfully vaccinated do not need to be tested for HBsAg; however, those patients who have low or no levels of anti-HBs should be tested for HBsAg monthly. The frequency of patient testing for anti-HBs also depends on whether the patient is unvaccinated or vaccinated, as shown in Table 2.

No evidence was found to indicate that these conclusions would not also apply to patients undergoing PD.

Summary

Patients with advanced chronic renal failure develop uremia, which is uniformly fatal if not treated by either RT or RD. At this time in the United States, there are about 200,000 individuals receiving dialysis at a cost of $7 billion a year. The precise biochemical reasons why uremia develops and why dialysis is partially successful are not fully understood.

Many tests are performed on uremic patients to monitor their clinical course and the success of dialysis. The tests to judge the adequacy of dialysis

and the amount and type of dialysis for individual patients (the DP) may not be optimal and are the subject of further study and modification.

Some of these tests are classified in HCFA's *Medicare Coverage Issues Manual*[4] as "other than routinely performed." Among these are NCTs, ECGs, chest x-rays, and tests for the presence of hepatitis B antigens and antibodies. At this time, HCFA allows reimbursement for the routine performance of these tests at specified frequencies. There is no reliable evidence to support the usefulness of such tests performed routinely in patients with ESRD. Only in the case of NCT is there a substantial literature that addresses the usefulness of this type of test in a manner specific for ESRD.

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